## REMARKS

Claims 1-13 and 15 are pending in this application. By this amendment, claims 1 and 2 are amended, and new claims 16-20 are added. Following entry of this amendment, claims1-13 and 15-20 will be pending. No new matter is added. Support for the amendments is found throughout the specification and originally filed claims, including at, e.g., the specification at page 4, line 25, and page 31, lines 28-30. Entry of this amendment is respectfully requested.

With respect to all new and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any objection and/or rejection made by the Office. Applicants expressly reserve the right to pursue prosecution of any subject matter not presently claimed in one or more future or pending continuation and/or divisional applications.

Applicants acknowledge the withdrawal of the objections to the specification and the rejections under 35 USC Section 112, second paragraph.

***IDS***

Applicants thank the Examiner for considering the PTO Form 1449 filed March 4, 2005. Applicants note that the individual references cited in references 37 and 38 have been individually submitted in prior Information Disclosure Statements.

***Priority***

The Examiner grants priority benefit to parent application PCT/US00/0434, but denies priority benefit to parent application PCT/US99/05028 (WO99/46281) on the ground that the Examiner was unable to locate information in that application relating to the use of PRO866 as an antiproliferative agent. As requested by the Examiner, page 275 of WO99/46281 is enclosed herewith as Appendix A. Lines 1-23 describe the antiproliferative assay, and the activity of PRO866 in the assay is noted in line 23. Accordingly, Applicants submit that the present application is entitled to at least the priority benefit of PCT/US99/05028 (WO99/46281), filed March 8, 1999. Applicants respectfully request that the Examiner withdraw the denial of the priority claim.

***Rejections Under 35 U.S.C. § 102***

1. Claims 1-9, 12-13 and 15 remain rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Number 6,682,902 (Harkins et al.). Applicants respectfully traverse this rejection.

The Examiner accords Harkins the 102(e) date of Dec. 16, 1999. By contrast, as explained in the section entitled "priority", the present application claims the benefit of parent

applications USSN 60/081,071 filed April 7, 1998, PCT/US99/05028, filed March 8, 1999, and PCT/US00/04341, filed February 18, 2000. Accordingly, Harkins is not a 102(e) reference to the present application, and withdrawal of this rejection is respectfully requested.

**2.** Claims 1-9, 12-13 and 15 remain rejected under 35 U.S.C. § 102(b) as allegedly anticipated by WO 98/45442 (Sheppard et al.). Applicants respectfully traverse this rejection.

Sheppard is not prior art to the present application. As noted above, the present application claims the benefit of parent applications USSN 60/081,071 filed April 7, 1998, PCT/US99/05028, filed March 8, 1999, and PCT/US00/04341, filed February 18, 2000. By contrast, Sheppard published on Oct. 15, 1998, and thus, is not a 102(b) reference to the present application. Withdrawal of this rejection is respectfully requested.

**3.** Claims 1-8, 12-13 and 15 remain rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 5,871,969 (Hastings, et al.). Applicant respectfully traverse the rejection.

Applicants note that claims 1 and 2 have been amended and now recite that the antibody specifically binds a polypeptide having at least 99% amino acid sequence identity to (claim 1), or comprising (claim 2): (a) the amino acid sequence shown in Figure 8 (SEQ ID NO:8); (b) the amino acid sequence shown in Figure 8 (SEQ ID NO:8), lacking its associated signal peptide; (c) an amino acid sequence encoded by the nucleotide sequence shown in Figure 3 (SEQ ID NO:3); (d) an amino acid sequence encoded by the full-length coding sequence of the nucleotide sequence shown in Figure 3 (SEQ ID NO:3); or (e) an amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209750. New claims 16-20 also recite the phrase "specifically bind". Support for the amendment is found at least at page 4, lines 35-36 of the specification.

A prima facie case has not been made. An antibody to the polypeptide of the Hastings patent would not specifically bind to a polypeptide recited by claims 1 and 2 of the present application, because "specific binding", as used in the present application and well-understood in the art, means that the antibody binds a particular polypeptide and does not substantially bind to any other polypeptide.

The term "specifically binds to" is defined in the present application at page 31, lines 28-30. The definition states that "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a

particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

Applicants contend that the pending claims are directed towards antibodies that:

(1) specifically bind one class of polypeptides: polypeptides having at least 99% amino acid sequence identity to (claim 1), or comprising (claim 2): (a) the amino acid sequence shown in Figure 8 (SEQ ID NO:8); (b) the amino acid sequence shown in Figure 8 (SEQ ID NO:8), lacking its associated signal peptide; (c) an amino acid sequence encoded by the nucleotide sequence shown in Figure 3 (SEQ ID NO:3); (d) an amino acid sequence encoded by the full-length coding sequence of the nucleotide sequence shown in Figure 3 (SEQ ID NO:3); or (e) an amino acid sequence encoded by the full-length coding sequence of the cDNA deposited under ATCC accession number 209750, and

(2) do not substantially bind to any other polypeptide.

Accordingly, any antibody that binds both the amino acid sequences of the Hastings patent and the polypeptides recited in claims 1 and 2 would be outside the scope of this claim. Withdrawal of this rejection is respectfully requested.

Moreover, Applicants note that the Examiner has made an improper inherency rejection. According to the Examiner, the claimed antibodies are disclosed in the cited references, absent factual evidence to the contrary. Applicants respectfully point out that the Examiner has not made a prima facie case for inherent anticipation under 35 U.S.C. § 102, and has not provided the required basis for alleging inherent anticipation. As such, the rejection does not stand and Applicants are not required to present any contrary evidence, as requested by the Examiner.

**4.** Claims 1-8, 12-13 and 15 remain rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent Number 6,287,777 (Sytkowski, et al.). Applicants respectfully traverse this rejection.

Sytkowski et al. is not prior art to the present application. The Examiner accords Sytkowski the 102(e) date of Aug. 10, 1999. By contrast, the present application claims the benefit of parent applications USSN 60/081,071 filed April 7, 1998, PCT/US99/05028, filed March 8, 1999, and PCT/US00/04341, filed February 18, 2000. Accordingly, Sytkowski is not a 102(e) reference to the present application, and withdrawal of this rejection is respectfully requested.

**5.** Claims 1-8, 12-13 and 15 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by WO 99/46281 (Wood et al.). Applicants respectfully traverse this rejection.

Wood et al. is not prior art to the present application. As noted above, the present application claims the benefit of parent applications USSN 60/081,071 filed April 7, 1998, PCT/US99/05028, filed March 8, 1999, and PCT/US00/04341, filed February 18, 2000. By contrast, Wood et al. published on Sept. 16, 1999, and thus, is not a 102(b) reference to the present application. Withdrawal of this rejection is respectfully requested.

**6.** Claims 1 and 2 are rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Higashijima et al, Developmental Biology 192:211-227, 1997. Applicants respectfully traverse the rejection.

A prima facie case has not been made because an antibody to the polypeptide of the Higashijima would not specifically bind to a polypeptide recited by claims 1 and 2 of the present application, because "specific binding", as used in the present application and well-understood in the art, means that the antibody binds a particular polypeptide and does not substantially bind to any other polypeptide as explained in section 3, above.

In addition, according to the Examiner, use of the peptide corresponding to amino acids disclosed in Hagashijima results in generation of an antibody as presently claimed. Applicants respectfully point out that the Examiner has not made a prima facie case for inherent anticipation under 35 U.S.C. § 102, and has not provided the required basis for alleging inherent anticipation.[1] As such, the rejection does not stand and Applicants are not required to present any contrary evidence.

The Examiner has presented no evidence that an antibody that recognizes the zebrafish peptide would necessarily recognize that epitope in the polypeptides recited in claims 1 or 2. The zebrafish protein recognized by the antibody of Higashijima has only limited sequence identity to SEQ ID NO: 8 of the present application, and thus may fold differently, adopt a different 3 dimensional conformation, have different post-translational modifications and the like. Thus, epitope recognized by the antibodies of Higashijima is not necessarily accessible for binding in the antibodies of the present claims. As such, prompt withdrawal of this rejection is respectfully requested.

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[1] Inherency requires that all of the limitations of the claims must be necessarily, inevitable, and always result from the prior art disclosure, and would be so recognized by one of ordinary skill in the art. M.P.E.P. § 2112. Moreover, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." Id. (quoting In re Oelrich, 212 USPQ 323, 326 (CCPA 1981). See also Continental Can Co. v. Monsanto Co., 20 USPQ2d 1746, 1749 (Fed. Cir. 1991); Mehl-Biophile Int'l Corp. v. Milgraum, 52 USPQ2d 1303, 1306 (Fed. Cir. 1999).

***Rejections Under 35 U.S.C. 103(a)***

Claims 10 and 11 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Harkins or Sheppard, either one in view of U.S. Patent No. 5,208,020 (Chari et al.). Applicants respectfully traverse this rejection.

As noted above, neither Harkins nor Sheppard is prior art to the present application. Thus, none of these references may be considered in this 103 rejection. Chari is cited merely for maytansinoid or calicheamicin toxins. However, Chari does not disclose the claimed antibodies. Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

Claims 3-9, 12-13 and 15 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Higashijima et al., Developmental Biology 192:211-227, 1997, in view of Lal et al., U.S. Patent No. 5,932,445. Applicants respectfully traverse this rejection.

As noted above, Higashijima does not teach the claimed antibodies. Lal is cited as allegedly disclosing that production of monoclonal, fragment, chimeric, radioactive and labeled antibodies was routine in the art. However, Lal does not disclose the claimed antibodies. Accordingly, Applicants submit that a prima facie case of obviousness has not been made. Withdrawal of this rejection is respectfully requested.

## SUMMARY

Applicants believe that this application is now in condition for allowance and respectfully requests that the outstanding rejections be withdrawn and this case passed to issue. No new matter has been introduced, and entry of these amendments is respectfully requested. The Examiner is invited to contact the undersigned at (650) 467-6222 in order to expedite the resolution of any remaining issues.

In the unlikely event that this document is separated from the transmittal letter or if fees are required, Applicants petition the Commissioner to authorize charging our Deposit Account 07-0630 for any fees required or credits due and any extensions of time necessary to maintain the pendency of this application.

Respectfully submitted,
GENENTECH, INC.

Date: 12/21/05

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EXAMPLE 113: In Vitro Antiproliferative Assay

The antiproliferative activity of various PRO polypeptides was determined in the investigational, disease-oriented *in vitro* anti-cancer drug discovery assay of the National Cancer Institute (NCI), using a sulforhodamine B (SRB) dye binding assay essentially as described by Skehan et al., *J. Natl. Cancer Inst.* 82:1107-1112 (1990). The 60 tumor cell lines employed in this study ("the NCI panel"), as well as conditions for their maintenance and culture *in vitro* have been described by Monks et al., *J. Natl. Cancer Inst.* 83:757-766 (1991). The purpose of this screen is to initially evaluate the cytotoxic and/or cytostatic activity of the test compounds against different types of tumors (Monks et al., *supra*; Boyd, *Cancer: Princ. Pract. Oncol. Update* 3(10):1-12 [1989]).

Cells from approximately 60 human tumor cell lines were harvested with trypsin/EDTA (Gibco), washed once, resuspended in IMEM and their viability was determined. The cell suspensions were added by pipet (100 μL volume) into separate 96-well microtiter plates. The cell density for the 6-day incubation was less than for the 2-day incubation to prevent overgrowth. Inoculates were allowed a preincubation period of 24 hours at 37°C for stabilization. Dilutions at twice the intended test concentration were added at time zero in 100 μL aliquots to the microtiter plate wells (1:2 dilution). Test compounds were evaluated at five half-log dilutions (1000 to 100,000-fold). Incubations took place for two days and six days in a 5% $CO_2$ atmosphere and 100% humidity.

After incubation, the medium was removed and the cells were fixed in 0.1 ml of 10% trichloroacetic acid at 40°C. The plates were rinsed five times with deionized water, dried, stained for 30 minutes with 0.1 ml of 0.4% sulforhodamine B dye (Sigma) dissolved in 1% acetic acid, rinsed four times with 1% acetic acid to remove unbound dye, dried, and the stain was extracted for five minutes with 0.1 ml of 10 mM Tris base [tris(hydroxymethyl)aminomethane], pH 10.5. The absorbance (OD) of sulforhodamine B at 492 nm was measured using a computer-interfaced, 96-well microtiter plate reader.

A test sample is considered positive if it shows at least 50% growth inhibitory effect at one or more concentrations. The following PRO polypeptides gave positive results in at least one tumor cell line: PRO181, PRO237, PRO526, PRO362 and PRO866.

EXAMPLE 114: Gene Amplification

This example shows that genes encoding various PRO polypeptides are amplified in the genome of certain human cancers. Amplification is associated with overexpression of the gene product, indicating that the PRO polypeptide is a useful target for therapeutic intervention in certain cancers such as colon, lung and other cancers. Therapeutic agent may take the form of antagonists of PRO polypeptide-encoding genes, for example, murine-human chimeric, humanized or human antibodies against the PRO polypeptide.

The starting material for the screen was genomic DNA isolated from a variety cancers. The DNA is quantitated precisely, e.g., fluorometrically. As a negative control, DNA was isolated from the cells of ten normal healthy individuals which was pooled and used as assay controls for the gene copy in healthy individuals (NorHu).

The 5' nuclease assay (for example, TaqMan™) and real-time quantitative PCR (for example, ABI Prizm 7700 Sequence Detection System™ (Perkin Elmer, Applied Biosystems Division, Foster City, CA)), were used to find genes potentially amplified in certain cancers. The results were used to determine whether the DNA encoding the PRO polypeptide is over-represented in any of the lung and colon cancers that were screened. The result was reported in Delta CT units. One unit corresponds 1 PCR cycle or approximately a 2-fold amplification relative to normal, two units corresponds to 4-fold, 3 units to 8-fold and so on. Quantitation was obtained using primers and